Amendments to the Specification:

Please replace paragraph [0086] with the following amended paragraph:

[0086] ~~Figure 1 (A, B)~~Figures 1A-B (SEQ ID NO:1) ~~shows~~ show the nucleotide sequence of RAP-2, the start and stop codons being underlined. The arrow indicates the start of the 1.5 Kb clone obtained by two hybrid screening~~;~~.

Please replace paragraph [0087] with the following amended paragraph:

[0087] ~~Figure 2 (A, B)~~Figures 2A-B (SEQ ID NO:2) ~~shows~~ show the nucleotide sequence of clone #41072 (see Example 1), the start and stop codons being underlined~~;~~.

Please replace paragraph [0088] with the following amended paragraph:

[0088] Figure ~~3 A~~3A (/1, /2) shows the deduced amino acid sequences of the human (20.4 full (SEQ ID NO:4) and *Human shrt* (SEQ ID NO:7)) and murine (NEMO full (SEQ ID NO:5) and *Mouse part* (SEQ ID NO:6)) splice variants of RAP-2 and ~~B~~ Figure 3B (/1, /2) ~~shows~~ compares the human 20.4 full sequence (SEQ ID NO:4) with the published sequence of FIP-2 (SEQ ID NO:8) aligned using the software package available at the BCM Search Launcher (Baylor College of Medicine, Houston, TX). Homologous amino acids are boxed, identical amino acids are gray-shaded. Asterisks in ~~(B)~~Figure 3B denote a putative leucine-zipper (LZ)-like motif in FIP-2.

Please replace paragraph [0089] with the following amended paragraph:

[0089] ~~Figure 4~~Figures 4A-C ~~describes~~describe the molecular characterization of RAP-2. In ~~A~~ Figure 4A, Northern blot hybridization of Human MTN Blot I (Clontech) with a DNA fragment of RAP-2 is shown. In ~~B~~ Figure 4B, RAP-2 binding to RIP is analyzed as detailed in Example 3. In ~~C~~ Figure 4C, NIK-RAP-2 interaction was detected as in ~~(B)~~ Figure 4B, except that anti-FLAG antibodies were used for Western blotting followed by immunoprecipitation with anti-His6. An arrow marks the position of the immunoprecipitated proteins.

Please replace paragraph [0090] with the following amended paragraph:

[0090] ~~Figure 5 is a~~Figures 5A-B are graphic ~~representation~~ representations of the massive downregulation of NF-κB and c-Jun activation by various stimuli, by ectopic expression of RAP-2 as described in Example 4. HEK-293T cells were transiently transfected with the reporter plasmid (HIVLTR-Luc or CMV-Luc for NF-κB ~~(A)~~ (Figure 5A) and GAL4-Luc for c-Jun ~~(B)~~ (Figure 5B) activation assays), and with an expression vector for the indicated inducer and either the empty vehicle (pcDNA3 - marked alone in the figure) or a plasmid encoding the full-length RAP-2 (pcRAP-2 - marked plus in the figure). Activation of the reporter gene luciferase activity is expressed in Relative Luciferase Units (R.L.U.).

Please replace paragraph [0091] with the following amended paragraph:

[0091] ~~Figure 6 shows~~Figures 6A and 6B show that RAP-2 exhibits similar repressive behavior toward NF-κB and c-

Jun in a wide concentration range. TRAF2 was transiently expressed in HEK-293T cells along with the various indicated amounts of either pcRAP-2 (sense) or pcRAP-2-a/s (antisense) constructs. For assessment of NF-κB ~~(A)~~ (Figure 6A) and c-Jun ~~(B)~~ (Figure 6B) activation pHIVLTR-Luc and pGAL4-Luc reporter plasmids were included respectively. Luciferase assay was performed as described for Figure 5 in Example 4.

Please replace paragraph [0092] with the following amended paragraph:

[0092] ~~Figure 7 shows~~Figures 7A-C show that RAP-2 strongly potentiates signal-induced phosphorylation of c-Jun without interfering with JNK1/2 activation level.

Please replace paragraph [0093] with the following amended paragraph:

[0093] ~~(A) Total~~In Figure 7A, total cellular lysates of HEK-293T cells, transfected with the indicated expression constructs together with either pcDNA3-carrier denoted in the figure by a minus sign (-) or with pcRAP-2 denoted in the figure by a plus sign (+), were identified by Western blot analysis with anti phospho-Jun antibodies as described in Example 5. The control membrane shown on the lower panel (Figure 7A(2)) was re-probed with anti-total-c-Jun Abs (NEB) ~~.~~.

Please replace paragraph [0094] with the following amended paragraph:

[0094] ~~(B) Activated~~In Figure 7B, activated JNK1/2 from HEK-293T cells transfected with either pcDNA3 or pcRAP-2, treated with hrTNFα for increasing periods of time were

detected by Western blotting of total lysates with Abs to phospho-JNK as detailed in Example 5.

Please replace paragraph [0095] with the following amended paragraph:

[0095] ~~(C)~~ In Figure 7C, HEK-293T cells, co-transfected with empty vector, pcRAP-2 and pcRIP in various combinations together with HA-JNK1-expressing plasmid. JNK1 was then immunoprecipitated via its N-terminal HA-tag and its ability to phosphorylate bacterially-produced purified GST-Jun was determined in an *in vitro* kinase assay. Reaction products were analyzed by SDS-PAGE. GST-Jun is marked by an arrowhead.

Please replace paragraph [0096] with the following amended paragraph:

[0096] ~~Figure 8 shows~~Figures 8A-B show that RAP-2 does not compete with NF-κB and AP-1 for binding to DNA. HEK-293T were transfected with the indicated proteins either alone (-) or together with pcRAP-2 (+). Nuclear extracts prepared from the cells were co-incubated with the 32P-labeled oligonucleotides comprising classical recognition sequences for AP-1 ~~(A)~~ (Figure 8A) or NF-κB ~~(B)~~ (Figure 8B).

Please replace paragraph [0097] with the following amended paragraph:

[0097] ~~Figure 9 shows~~Figures 9A-B show that RAP-2 affects the basal level of NF-κB in HEK-293T (Figure 9A) and HeLa (Figure 9B) cells transiently transfected with variable amount of either RAP-2 (sense) or RAP-2-antisense (a/s). All

manipulations were performed as described for Figure 6 in Example 4.

Please replace paragraph [0098] with the following amended paragraph:

[0098] ~~Figure 10 (A, B)~~Figures 10-B (SEQ ID NO: 3) ~~shows~~ show the partial nucleotide sequence of clone #10.

Please replace paragraph [0099] with the following amended paragraph:

[0099] ~~Figure 11 shows~~Figures 11A-B show the functional properties of serial deletions of RAP-2. In ~~A~~Figure 11A, there is a schematic representation of the consecutive C-terminal deletions of RAP-2. All truncations share the intact RAP-2 N-terminus, while their C-terminal ends are designated by arrowheads. The RIP, NIK, IKKβ and TIP60 binding region is underlined. Three hatched boxes correspond to the putative leucine-zipper-like motifs. ~~B~~ Figure 11B shows the effect of overexpression of the deletion constructs described in A on NF-κB activation in HEK-293T cells by RelA, TRAF2 TNF and NIK using the HIV-LTR luciferase reporter plasmid for NF-κB. Activation of the reporter gene luciferase activity is expressed in Relative Luciferase Units (R.L.U.).

Please replace paragraph [0100] with the following amended paragraph:

[0100] ~~Figure 12: shows~~Figures 12A-B show mapping of RAP-2 functional and binding regions.

Please replace paragraph [0101] with the following amended paragraph:

[0101] ~~(A) Various~~ In Figure 12A, various deletions of RAP-2 were tested for their ability to bind the indicated proteins within transfected yeast (odd columns) and mammalian HEK-293T cells (even columns). The two rightmost columns show the ability of the same deletions transfected at high amounts as detailed in example 9 into HEK-293T cells, to inhibit NF-κB activation and potentiate c-Jun hyperphosphorylation (c-Jun) in response to TNF-α treatment. Boldness of the crosses is proportional to the intensity of a given effect. Asterisks indicate that the observed effects of the labeled constructs towards Rel-A stimulation are distinct (see Figure 11B).

Please replace paragraph [0102] with the following amended paragraph:

[0102] (~~B) Summary~~Figure 12B is a summary of the chart representing localization of the binding (upper part) and functional (bottom part) regions of RAP-2 as inferred from the deletion analysis shown in ~~(A)~~Figure 12A, aligned along the protein backbone. The hatched parts indicate possible location of borders of the corresponding minimal regions.

Please replace paragraph [0103] with the following amended paragraph:

[0103] ~~Figure 13:~~Figure 13 shows that ser-148 in RAP-2 is essential for its ability to induce c-Jun hyper phosphorylation at ser-63.

Please replace paragraph [0171] with the following amended paragraph:

[0171] A non-limiting example of how peptide inhibitors of the RAP-2-RIP interaction would be designed and screened is based on previous studies on peptide inhibitors of ICE or ICE-like proteases, the substrate specificity of ICE and strategies for epitope analysis using peptide synthesis. The minimum requirement for efficient cleavage of peptide by ICE was found to involve four amino acids to the left of the cleavage site with a strong preference for aspartic acid in the P1 position and with methylamine being sufficient to the right of the P1 position (Sleath et al, 1990; Howard et al, 1991; Thornberry et al, 1992). Furthermore, the fluorogenic substrate peptide (a tetrapeptide), acetyl-Asp-Glu-Val-Asp-a-(4-methyl-coumaryl-7-amide) (SEQ ID NO:9), abbreviated Ac-DEVD-AMC (SEQ ID NO:9), corresponds to a sequence in poly (ADP-ribose) polymerase (PARP) found to be cleaved in cells shortly after FAS-R stimulation, as well as other apoptopic processes (Kaufmann, 1989; Kaufmann et al, 1993; Lazebnik et al, 1994), and is cleaved effectively by CPP32 (a member of the CED3/ICE protease family) and MACH proteases (and likewise also possibly by G1 proteases - see for example co-owned co-pending IL 120367).

Please replace paragraph [0217] with the following amended paragraph:

[0217] Using the two-hybrid screen with RIP as the bait (see e.g., Fields and Song, 1989, WO/96/18641) in a B-cell library, a clone of about 1.5 Kb size was isolated. This 1.5 Kb clone (see arrow in Figs. 1 (residues 437-2009 of SEQ

ID NO:1) and 2 (residues 461-2034 of SEQ ID NO:2)) was used for screening a phage cDNA library, yielding an about 2.0 Kb clone, the sequence of which is shown in Fig. 1.

Please replace paragraph [0218] with the following amended paragraph:

[0218] By employing EST matching with the sequence of the 1.5 Kb clone, an EST fragment was obtained which constitutes the 3' end of I.M.A.G.E. consortium clone #41072 (Research Genetics Institute). Of this clone, which originates from a fetal brain library, only two small sequence fragments at its 3' and 5' ends are published. After obtaining the clone it was sequenced and it turned out that even these published sequence fragments contained errors. The sequenced clone (Fig. 2 (SEQ ID NO:2)), was found to be identical to the clone of Fig. 1 (SEQ ID NO:1) in its coding region, but showed differences in the 5'- noncoding region. It is therefore assumed that both cDNAs are alternatively spliced forms of the same gene.

Please replace paragraph [0222] with the following amended paragraph:

[0222] This clone, as noted above, was used to screen a phage cDNA library and an EST databank. It can be seen from Figs. 1 and 2 (SEQ ID NO:1 and 2, respectively) that the coding sequences of the two clones are identical, while the 5'-non coding regions differ. Thus we are probably concerned with alternatively spliced forms. The clones are of about 2.0 Kb with an ORF (open reading frame) of about 1.5 Kb,

which account for a molecular weight of about 50 Kd for the protein itself. The deduced amino acid sequence of RAP-2 is shown in Figure 3 (SEQ ID NO:4).

Please replace paragraph [0223] with the following amended paragraph:

[0223] Analysis of the above sequences of the RAP-2 clone and sequences in the 'dbest' database, Human Genome Database level 1 and GenBank database revealed that the RAP-2 sequence was a unique (novel) sequence as no known sequence showed any significant homology to this RAP-2 sequence. After filing of IL 123758, from which this application claims priority, Yamaoka S. et al, 1998, reported the characterization of a murine cDNA encoding a 48kD protein, which was designated NEMO (for NF-κB Essential Modulator) (SEQ ID NO:5). (See background)

Please replace paragraph [0224] with the following amended paragraph:

[0224] Additional database (*in silico*) searches identified FIP-2 (SEQ ID NO:8) - a protein with unknown functions originally cloned, by Li Y. et al (1998, see background).

Please replace paragraph [0225] with the following amended paragraph:

[0225] As can be seen from the global alignment of the RAP-2 (SEQ ID NO:4) and the FIP-2 (SEQ ID NO:8) sequences (Figure 3B), the degree of overall similarity is fairly low (it is therefore not surprising the sequence was not

identified using scans based on global algorithms). The homology between RAP-2 and FIP-2 increases towards the C-terminus of the proteins, culminating in virtual identity of the C-terminal 30 amino acids. Noteworthy, beside the latter region, the putative LZ-motif in FIP-2 is largely preserved in RAP-2 (except for an Ile/Ala substitution).

Please replace paragraph [0226] with the following amended paragraph:

[0226] An additional shorter RAP-2 cDNA of approximately 0.5kb was also identified (ID: 1469996) and which will be designated hereafter *Human shrt* (SEQ ID NO:7). This variant comprised coding sequence "blocks" deriving from several remote regions of the 1.5kb "full" cDNA, probably derived from alternative splicing of the same gene.

Please replace paragraph [0228] with the following amended paragraph:

[0228] A similar search of the mouse ESTs collection established at TIGR revealed a partial cDNA of 1.6kb (*Mouse part.* ID:761011, Figure 3 (SEQ ID NO:6)) probably corresponding to the mouse RAP-2, since it is virtually identical (95%) to its human counterpart throughout the coding region (see Figure 3).

Please replace paragraph [0243] with the following amended paragraph:

[0243] Applying the full-length RAP-2 protein as bait in two-hybrid screen of a B-cell cDNA library, we have isolated a novel protein interacting with RAP-2 denoted

hereafter clone #10 or clone #10-encoded protein or RAT-binding protein #10 or RBP-10 (Figure 10) (SEQ ID NO:3). The original clone (about 2.2 kb) was found to encode a putative polypeptide of apparent MW of 60kDa. However, the putative ATG first codon is apparently missing from this sequence. Despite its considerable length, the obtained cDNA has therefore to be expanded further towards the 5' end to reconstitute the entire open reading frame.

Please replace paragraph [0248] with the following amended paragraph:

[0246] Several rounds of GenBank searches aiming at identification of close RBP-10-homologues led to the identification of F40F12.5 (accession number S42834) - a ~~hypotetical~~hypothetical protein from *C. Elegans*~~*C. Elegans*~~, to which no physiological role was assigned. Interestingly, F40F12.5 was found to display some similarity to several members of the widely conserved family of ubiquitin-directed proteases. These enzymes counterbalance the destructive effect of the ubiquitination machinery, which is known to be in charge of the majority of protein degradation events in a cell. While ubiquitin ligases are responsible for attaching the poly-ubiquitin tree to a protein predestined for degradation, ubiquitin proteases prevents an effective branching of the growing tree. Such presumption regarding the function of F40F12.5 based on the similarity to the above-mentioned ubiquitin-directed proteases however appears to be questionable as it has not yet been examined whether this

particular protein possesses any enzymatic activity toward ubiquitin polymers. Furthermore, a couple of points appear to make such a coincidence quite unlikely: